Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS)

A single-center RCT

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ABSTRACT

Background: Constraint-induced movement therapy (CIMT) is among the most developed training approaches for motor restoration of the upper extremity (UE).

Methods: Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS) was a single-blind phase II trial of CIMT during acute inpatient rehabilitation comparing traditional UE therapy with dose-matched and high-intensity CIMT protocols. Participants were adaptively randomized on rehabilitation admission, and received 2 weeks of study-related treatments. The primary endpoint was the total Action Research Arm Test (ARAT) score on the more affected side at 90 days after stroke onset. A mixed model analysis was performed.

Results: A total of 52 participants (mean age 63.9 ± 14 years) were randomized 9.65 ± 4.5 days after onset. Mean NIHSS was 5.3 ± 1.8; mean total ARAT score was 22.5 ± 15.6; 77% had ischemic stroke. Groups were equivalent at baseline on all randomization variables. As expected, all groups improved with time on the total ARAT score. There was a significant time x group interaction ($F = 3.1$, $p < 0.01$), such that the high intensity CIT group had significantly less improvement at day 90. No significant differences were found between the dose-matched CIMT and control groups at day 90. MRI of a subsample showed no evidence of activity-dependent lesion enlargement.

Conclusion: Constraint-induced movement therapy (CIMT) was equally as effective but not superior to an equal dose of traditional therapy during inpatient stroke rehabilitation. Higher intensity CIMT resulted in less motor improvement at 90 days, indicating an inverse dose-response relationship. Motor intervention trials should control for dose, and higher doses of motor training cannot be assumed to be more beneficial, particularly early after stroke. *Neurology*® 2009;73:195–201

GLOSSARY

ADC = apparent diffusion coefficient; **ADL** = activities of daily living; **ARAT** = Action Research Arm Test; **CIMT** = constraint-induced movement therapy; **DWI** = diffusion-weighted imaging; **FIM** = Functional Independence Measure; **NIHSS** = NIH Stroke Scale; **SIS** = Stroke Impact Scale; **TE** = echo time; **TI** = inversion time; **TR** = repetition time; **UE** = upper extremity; **VECTORS** = Very Early Constraint-Induced Movement during Stroke Rehabilitation.

Stroke is a leading cause of disability, primarily from motor impairments. Experimental restorative treatments include structured therapeutic activity and pharmacologic augmentation.[1] For the upper extremity (UE), constraint-induced movement therapy (CIMT) is among the most developed approaches. The basic principles of CIMT were first explored long ago[2] but interest has surged recently.[3,4] A phase III randomized controlled trial of CIMT initiated in the 3- to 9-month period after stroke onset found it superior to usual and customary care,[5] with persistent treatment response.[6]

The use of CIMT during the inpatient rehabilitation phase, if proven superior to conventional rehabilitation, has several rationales. Substantial rehabilitation resources are expended during this phase of care; more effective retraining might improve outcome without increasing cost. Inpatient rehabilitation is the earliest point where CIMT is practical; early application

Editorial, page 170

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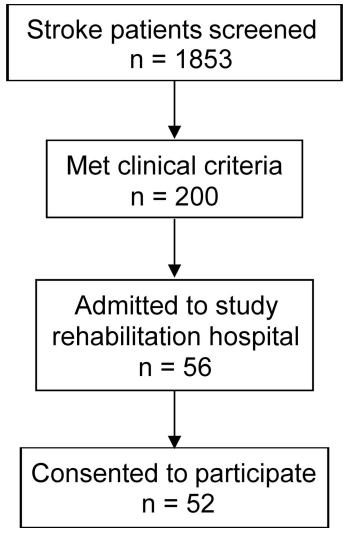
Figure 1 Screening algorithm



might preempt learned non-use,[7] and exploit any early window for best response to motor training.[8] Our pilot trial provided a basis[9] for further study.

METHODS

Participants. Acute stroke admissions at Barnes-Jewish Hospital in St. Louis, MO, were screened for study eligibility (figure 1). Three additional subjects were referred by outside neurologists. Subjects were included if they had 1) unilateral ischemic or hemorrhagic stroke (with confirmatory neuroimaging) within 28 days of admission to inpatient rehabilitation; 2) persistent hemiparesis, generally indicated by a score of 1–3 on the motor arm item of the NIH Stroke Scale (NIHSS)[10]; 3) proximal UE voluntary activity indicated by a score of ≥3 on the upper arm item of the Motor Assessment Scale,[11] but wrist and finger movement was not required; 4) preserved cognitive function as indicated by a) a score ≤1 on the consciousness and communication items of the NIHSS, b) the ability to perform two-step commands, and c) a score of <8 on the Short Blessed Memory Orientation and Concentration Scale[12]; and 5) no UE injury or conditions that limited use prior to the stroke. Exclusion criteria included 1) inability to give informed consent; 2) clinically significant fluctuations in mental status within 3 days of enrollment; 3) not independent prior to the index stroke (determined by scores <95 on the Barthel Index[13] or >1 on the Modified Rankin Scale[14]; 3) hemispatial neglect as determined by asymmetry >3 errors on the Star Cancellation Test[15]; 4) sensory loss ≥2 on the sensory item of the NIHSS; 5) not expected to survive 1 year due to other illnesses.

Interventions. VECTORS was a three-arm, single-blind, randomized controlled trial approved by the Washington University Human Studies Committee. The primary endpoint was the 90-day Action Research Arm Test (ARAT). Trained raters performed all blinded evaluations. Using baseline data collected on rehabilitation admission, we adaptively randomized[22] the groups balancing for age, total NIHSS score, pretest ARAT score on the affected side, and days from stroke onset to randomization.

Study treatments preempted occupational therapy and occurred 5 days per week for 2 consecutive weeks. Prespecified treatment protocols were developed based on our prior study and incorporated features of the EXCITE trial[5] manual. Subjects otherwise received routine inpatient interdisciplinary stroke rehabilitation. Research clinicians trained in study procedures provided all study-related treatments; all were licensed occupational therapists or supervised assistants. The study clinical team met weekly to assure adherence to protocols. Individual sessions and circuit-training techniques were used in all three study groups. The same group of therapists delivered both the experimental and control treatments. Prespecified protocols, developed for both the control and CIMT treatments, were focused primarily on basic activities of daily living (ADL) tasks required for discharge to the community.

The control treatment mimicked traditional occupational therapy, involving compensatory techniques for ADL, range of motion, and strengthening. This treatment consists of 1 hour of ADL retraining and 1 hour of UE bilateral training activities. Adaptive equipment and positioning devices were used; a prespecified cueing strategy neither encouraged nor discouraged the use of the hemiparetic UE. Massed practice, shaping, and constraint were prohibited.

The standard CIMT group received 2 hours of shaping therapy per day and wore a padded constraint mitten for 6 hours per day. The high-intensity CIMT group underwent 3 hours per day of shaping and wore the mitten for 90% of waking hours. This therapy consisted of performance of basic ADL together with supervised massed practice of skilled functional activities. These activities were graded per the study protocol by the treating occupational therapist to match the subject's motor performance. Increasing levels of demand were based on increases in strength and coordination of the involved joints. As participants achieved successful completion of self-care activities and 80% of the trials for each specific motor activity, the complexity or difficulty of these activities were increased to the next level. Subjects received extensive verbal and written feedback about their performance, including a review of the prior day's achievements, the day's proposed goals, and reinforcement of new gains and maintenance of prior gains in graphic and verbal form appropriate to the activities selected for the treatment session.

MRI substudy. In rodent brain infarct models, immediate immobilization of the unaffected forelimb causes lesion enlargement by an excitotoxic mechanism.[30,31] We therefore carried out an MRI safety substudy in nine subjects with ischemic stroke (two in the control group, four in the standard CIMT group, and three in the high-intensity CIMT group) to ascertain whether very early CIMT as employed in this study resulted in expansion of ischemic lesions. Since both acute ischemia and direct excitotoxic damage result in restricted diffusion by MRI, we determined if any new areas with abnormalities on diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) measurements developed during the course of CIMT.[38] An initial set of MRI scans was obtained between 1 and 22 days following stroke immediately prior to beginning the VECTORS treatments and a second set of scans 7–9 days later. MRI was performed with a 1.5-T Magnetom Sonata using an eight-channel head array and Syngo software. Following scout and auto alignment sequences, each subject had fluid-attenuated inversion recovery (repetition time [TR]/echo time [TE]/inversion time [TI] = 9,390/96/2,500, flip angle = 180, matrix = 192 × 256, 64 2-mm-thick slices, voxels = 1 × 1 × 2 mm), T2* (TR/TE = 2,700/61, flip angle = 90, acquisition matrix = 80 × 128, 60 2-mm-thick slices, voxels = 2 × 2 × 2 mm), and single-shot spin-echo echoplanar DWI (TR/TE = 10,000/80, flip angle = 90, acquisition matrix = 80 × 128, 72 2-mm-thick

slices, voxels = 2 × 2 × 2 mm, b = 0 and b = 800 mm^2/s) for DWI and ADC measurements. Images for each subject were coregistered using Automated Image Registration software (AIR 3.08, Roger Woods, UCLA). Subtraction images of coregistered DWI and ADC image pairs for each subject were visually examined for new areas of DWI or ADC change. In addition, any voxels within the area of infarction for which DWI intensities increased by at least 40% and ADC values decreased by at least 10% between the first and second scans were identified. These are conservative cutoffs based on a study that found mean DWI intensities were at least 90% greater and mean ADC intensities were at least 17% lower than normal within the first 7 days following cerebral infarction.[23] Scans from four subjects with intracerebral hemorrhages were excluded from the analysis because of the large changes in DWI/ADC signals for clotted blood that occur over time.

Objectives. Our objective was to examine whether CIMT was superior to an equivalent amount of traditional Occupational Therapy, and whether CIMT treatment effects would be dose dependent.

Outcomes. ***NIH Stroke Scale.*** The NIH Stroke Scale (NIHSS)[10] assesses cognitive, sensory, and motor impairments as an indicator of overall stroke severity.

Action Research Arm Test. The total ARAT[16] score in the more affected UE was the primary dependent measure. The ARAT assesses UE functional limitations with four ordinal subscales: grasp, grip, pinch, and gross movement. Item scores are summed to create subtest and full-scale scores; the maximum score of 57 indicates normal performance.

Functional Independence Measure. The Functional Independence Measure (FIM) is an 18-item disability measure.[17] All evaluators in this study were certified by the Uniform Data System. During the inpatient stay, the FIM was scored based on performance; after discharge, we used the Fone Fim[18] format developed for telephone administration of the standard FIM items. We created a FIM Upper Extremity Score by summing the 5 FIM items requiring significant hand and arm use.

The Stroke Impact Scale (hand function subscale). The five-item hand function subscale of the Stroke Impact Scale[19] (SIS) assesses hand strength, dexterity, and fine and gross motor ability associated with the ability to complete functional tasks. Higher scores indicate greater function and life satisfaction.

Pain ratings. The Wong-Baker Faces Scale was used to assess pain in the affected shoulder at days 0, 14, and 90[20] and during treatment.

Depression. The Geriatric Depression–15 Scale[21] was used to assess depression at days 0, 14, and 90. Scores below 5 are normal.

Statistical methods. SAS Version 9 for Windows was used. A modified intent to treat approach was used, with all available data used for all analyses. One-way analyses of variance were computed to verify the effects of the adapted randomization procedure and to ensure that age, stroke severity, and initial arm function were equivalent across the groups. We hypothesized that subjects randomized to 14 days of standard intensity or high-intensity CIM therapy would have greater improvement in motor function from baseline to 90 days after stroke than subjects randomized to traditional therapy and that they would be more independent in activities of daily living at 90 days after stroke. The total ARAT on the more affected side was the primary dependent measure. Group comparisons were performed with Proc Mixed, a generalization of the standard linear model (GLM) procedure to determine if there were significant main effects for groups and time and a group x time interaction. Random coefficient regression is used to examine the response functions of each treatment group over time. Repeated measures analysis of variance models were fit for each dependent measure with group assignment (control, standard CIMT, and high-intensity CIMT) as the between-subject factor and time of assessment (baseline, day 14, and day 90) as the within-subject factor. Least-square means adjusted for randomly missing values were computed by group for each time of testing. Type 3 tests of fixed effects were used for hypothesis testing. If the group x time interactions were significant ($p < 0.05$) preplanned comparisons were computed to examine pairwise differences among the three treatment groups. A futility analysis was conducted after 3 years of active subject recruitment. The analysis, completed by the project statistician, confirmed the study was adequately powered with 52 subjects to test the hypothesis.

RESULTS Figure 1 shows the CONSORT diagram of participant recruitment. Fifty-two individuals were randomized and table 1 presents their baseline characteristics. There were no significant differences on these variables across the treatment groups. There were no significant differences between groups in medical comorbidities: 10% had prior stroke, 65% had hypertension, 23% had diabetes, 6% had atrial fibrillation, and 10% had a history of myocardial infarction. None was on renal dialysis. Rehabilitation length of stay was 22.3 ± 7.1 days.

All but two participants were available for assessment at the 90-day primary endpoint. ARAT total and subtest scores for the affected arm are presented in table 2. The primary test of the study hypothesis is the comparison across groups of the slopes of the total ARAT scores from baseline to day 90 (group x time). The overall main effect for treatment groups was not significant (group: $F = 0.50$, $p < 0.61$). As expected, total ARAT scores improved from baseline to 90 days for all groups (time: $F = 45.15$, $p < 0.0001$). There were no significant differences between the standard CIMT and control patients from baseline to day 14 or baseline to day 90 (table 2, figure 2). Unexpectedly, for high-intensity CIMT, a significant group x time interaction ($F = 3.06$, $p < 0.01$) was observed for the total ARAT when all three groups were compared. Contrary to the study hypothesis, high-intensity CIMT patients had significantly lower gains in total ARAT scores from baseline to day 90 than control patients ($p < 0.006$) or standard CIMT patients ($p < 0.01$). Group comparisons of baseline vs day 14 were similar; high-intensity CIMT patients performed less well than control patients ($p < 0.03$) or standard CIMT patients ($p < 0.003$) (see figure 2A).

The same analyses were computed for the ARAT subtests (table 2). All subtest scores increased significantly from baseline to day 90. A group x time inter-

Table 1 Baseline characteristics of study participants (n = 52) shown by group*

	Total sample (n = 52)	Control (n = 17)	Low CIMT (n = 19)	High CIMT (n = 16)
Age, y	63.9 ± 14	64.7 ± 14.6	62.8 ± 12.8	64.5 ± 15.5
Days since stroke	9.7 ± 4.6	10.4 ± 5.7	8.8 ± 3.1	9.94 ± 4.8
Total NIHSS	5.3 ± 1.8	5.5 ± 1.8	5.1 ± 1.8	5.31 ± 1.8
Total ARAT, impaired	22.5 ± 15.3	19.7 ± 13.9	22.7 ± 14.3	25.4 ± 18.0
FIM motor	57.8 ± 11.1	56.7 ± 12.2	57.1 ± 9.5	59.8 ± 12.1
% Female	60	65	68	44
Race, %				
Caucasian	42	47	37	44
African American	57	53	58	56
Affected side, % R	52	52.9	47.4	56.3
% Dominant side affected	44.2	41.2	31.6	62.5
% Prior stroke	10	12	11	6
Stroke lesion				
% Ischemic	77	76	74	81

*No significant differences were found between groups for any demographic or clinical variable.
CIMT = constraint-induced movement therapy; NIHSS = NIH Stroke Scale; ARAT = Action Research Arm Test; FIM = Functional Independence Measure.

action was observed for the ARAT pinch subtest ($p < 0.03$). Pinch scores were highest in the standard CIMT group at day 14 and day 90 and lowest for the high-intensity CIMT pinch scores at day 90. The group x time interactions for the ARAT grip and gross motor subtests approached but did not reach statistical significance ($p < 0.06$). High-intensity CIMT patients had the lowest scores on these subtests at day 14 and day 90.

We evaluated the effects of standard or high-intensity CIMT on activities of daily living with the FIM Upper Extremity Score and the SIS hand subscale (figures 2B and 2C). We found no significant differences across the three treatment groups for the FIM Upper Extremity Scale; all groups achieved similar gains in function ($p < 0.16$). Mean ratings for SIS Hand subscale varied by group over the two times of testing [$F(1,50) = 3.88$, $p = 0.02$]. The control group scores were higher at day 14, while the standard CIMT group reported the highest scores at day 90. The high-intensity CIMT group had significantly lower scores at day 90 ($p < 0.02$). Thus, CIMT was no more effective than the control treatment in ameliorating UE-related disability and the high-intensity CIMT group had significantly less improvement.

Mean pain scores were low (≤3 out of 10 possible points), and shoulder pain increased significantly from baseline to the 90-day endpoint [$F(2,49) = 4.01$, $p < 0.01$]. There were no significant differences among the three treatment groups [$F(2,49) = 0.22$, $p < 0.80$], and all were similar to the prevalence of shoulder pain in other cohorts.[24] Group means for the Geriatric Depression Scale were within the normal range for all three groups at all three time points.

The nine subjects in the MRI substudy were initially studied 1–22 (mean 13.2) days after onset and again 7–9 (mean 7.3) days later. Infarct volumes defined by thresholding the DWI/ADC ratio image ranged from 0.1–13.5 mL. Eight of the nine subjects (one control, four standard CIMT, and three high-intensity CIMT) showed no areas of DWI or ADC change upon visual inspection and had no voxels with changes in DWI or ADC signal intensities above threshold. Another control subject had five scattered voxels above threshold which could be attributed to imaging noise.

DISCUSSION During acute inpatient stroke rehabilitation, CIMT was not superior to an equal amount of traditional occupational therapy. Further, we found an inverted dose response effect, in which a higher dose of shaping and constraint led to significantly less UE motor improvement at 90 days. These striking results were consistent across all endpoints.

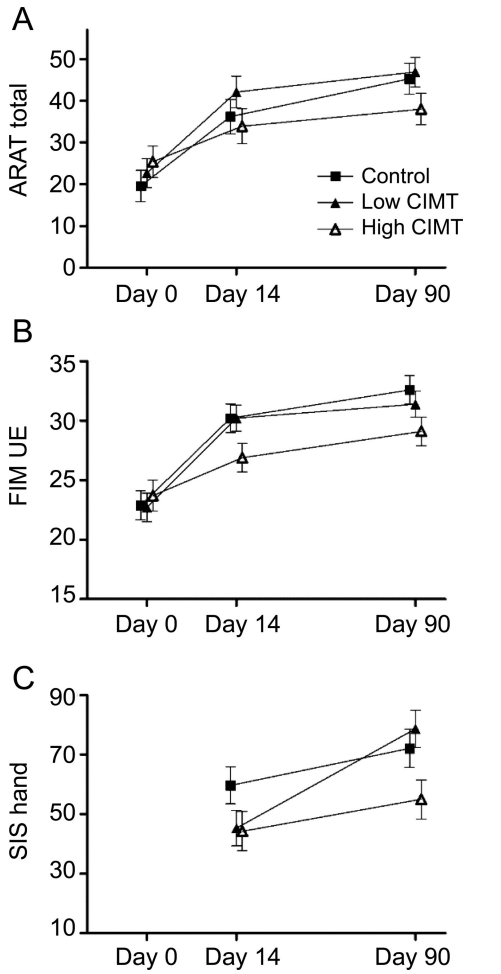
These results are consistent with other reports, particularly with studies in which control groups received equal amounts of therapy time. CIMT was found to be superior to an equal amount of neurodevelopmental treatment in a more clinically heterogeneous sample of chronic patients who were at least 1 year poststroke.[25] However, this superiority was limited to the subgroups with sensory loss and hemineglect, two groups excluded from VECTORS. A smaller acute study with a similar design using treatment sessions distributed over 3 weeks, and including subjects 2 weeks poststroke, found no difference in prespecified primary outcomes compared to a dose-matched control.[26] Our prior work found a benefit for CIMT compared to a dose-matched control, but the sample was much smaller and the randomized groups were not balanced on important clinical features.[9] A phase III trial of CIMT performed in the 3- to 9-month period poststroke demonstrated the ability of a CIMT program to improve UE motor function during that period after stroke when compared to the usual and customary care provided in the United States.[5] Because usual and customary care in the United States during this 3- to 9-month period involves far less motor training than that delivered to the CIMT group, the extent to which the benefit was related to the CIMT treatment paradigm, to a nonspecific effect of a higher dose of motor training, or to both[27] is unclear. Two other studies using a dose-matched control did find CIMT to be superior, but used a small sample[28] or a later time after stroke onset.[29]

Table 2 Least-square mean and standard errors of study outcomes

	Control	Low CIMT	High CIMT	F (df = 6,49)	p
Total ARAT*					
Day 0	19.65 ± 3.73	22.68 ± 3.52	25.43 ± 3.84	3.06	0.01
Day 14	36.20 ± 4.05	42.10 ± 3.82	33.93 ± 4.16		
Day 90	45.34 ± 3.68	46.86 ± 3.51	38.00 ± 3.76		
ARAT grip*					
Day 0	4.58 ± 0.88	5.00 ± 0.83	5.19 ± 0.90	2.16	0.06
Day 14	8.32 ± 0.87	9.31 ± 0.81	7.43 ± 0.89		
Day 90	9.79 ± 0.78	10.61 ± 0.74	8.37 ± 0.79		
ARAT pinch*					
Day 0	2.94 ± 1.26	4.73 ± 1.19	6.37 ± 1.30	2.61	0.03
Day 14	7.62 ± 1.68	10.58 ± 1.58	8.75 ± 1.72		
Day 90	12.96 ± 1.45	14.39 ± 1.39	10.00 ± 1.48		
ARAT grasp*					
Day 0	7.11 ± 1.34	7.31 ± 1.27	8.56 ± 1.38	1.52	0.19
Day 14	13.53 ± 1.40	14.21 ± 1.32	11.56 ± 1.43		
Day 90	14.33 ± 1.29	15.06 ± 1.23	12.94 ± 1.32		
ARAT gross motor*					
Day 0	4.88 ± 0.62	5.53 ± 0.58	5.31 ± 0.64	2.15	0.06
Day 14	7.00 ± 0.54	7.79 ± 0.50	6.19 ± 0.55		
Day 90	8.08 ± 0.52	8.26 ± 0.50	6.81 ± 0.53		
FIM upper extremity					
Day 0	22.88 ± 1.22	22.73 ± 1.15	23.69 ± 1.26	1.61	0.16
Day 14	30.23 ± 1.17	30.21 ± 1.11	26.93 ± 1.21		
Day 90	32.58 ± 1.15	31.41 ± 1.10	29.12 ± 1.16		
Stroke Impact Scale, hand and arm					
Day 0	NA	NA	NA		
Day 14	59.71 ± 6.21	45.26 ± 5.87	44.33 ± 6.61	3.88	0.02
Day 90	72.16 ± 6.37	78.65 ± 6.15	55.00 ± 6.63		

*More affected arm.
CIMT = constraint-induced movement therapy; ARAT = Action Research Arm Test; FIM = Functional Independence Measure.

Figure 2 (A–F) Mixed model analyses of ARAT total (A), FIM UE scores (B), and SIS hand function subscale (C)



Group means ± SD from the mixed model analyses on the ARAT total. ARAT = Action Research Arm Test; FIM = Functional Independence Measure; SIS = Stroke Impact Scale; CIMT = constraint-induced movement therapy.

Our finding of an inverted dose-response curve bears further comment, and we have considered several explanations. In rodent stroke recovery models, immediate casting of the unaffected forelimb has been reported to cause lesion enlargement[30] that is presumed excitotoxic[31] and is associated with a decrement in motor recovery.[32] We found no evidence for CIMT-caused lesion enlargement in a small MRI substudy. Shoulder pain and depression have both been reported to hinder stroke recovery.[33] However, self-reported pain and depression were not significantly different across the three study groups. Another possible explanation is fatigue or injury related to overtraining. Overtraining effects are best described in the resistance training literature, where effects of resistance loading and training volume have been studied in some detail.[34] The possibility of overtraining was recently described in another stroke rehabilitation study using different training modalities to improve gait[35]; in this case, however, progressive lower extremity strength training was an explicit intervention goal, an approach quite unlike CIMT. Yet another possibility is that increasing the time spent daily in shaping sessions by 50% effectively led to a change in practice schedule, from a "distributed" practice schedule to a more "blocked" schedule. There is a substantial motor learning literature suggesting that distributed practice schedules lead to better task learning and performance.[36,37] Thus the extra time spent by the high-intensity CIMT group actually may have interfered with motor learning.

NIHSS scores were relatively low in our sample, a consequence of enrolling cognitively capable persons who had some residual UE motor abilities. Eliminating persons with complete paralysis or severe disorders of consciousness, sensation, aphasia, or neglect

must result in NIHSS scores within the range of our study participants. Because all subjects otherwise received usual and customary care after the 14-day study treatment, data about treatments after discharge were not collected; CIMT was prohibited outside the study treatment period. Although this study used a relatively small sample, futility analysis indicated sufficient power to test the hypothesis.

Our results have two important implications. First, our finding that equal time of CIMT and conventional therapy were equally effective in ameliorating UE impairment and disability emphasizes the need for clinical trials with control groups that match therapy doses. Without such a control, the superiority of a specific training paradigm cannot be demonstrated. Second, we found significant dose effects for training, suggesting that motor training interventions, like drug interventions, can have dose-response effects. However, as with drugs, it appears possible that doses higher than an optimal range may be less effective than lower doses, and even detrimental. Establishing optimal therapy dosing may require determination of specific dose-response curves through clinical studies that directly test different doses of therapy. Given the large variety of results of timing and dose studies in rodent models of stroke recovery, we suggest that such studies must address specific time points after stroke onset.

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Statistical analysis was performed by J.P.M.

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DISCLOSURE

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REFERENCES

1. Dromerick AW, Lum PS, Hidler J. Activity-based therapies. NeuroRX 2006;3:428–438.
2. Franz SI, Sheetz MK, Wilson WW. The possibility of recovery of motor function in long standing hemiplegia. JAMA 1921;65:2150–2154.
3. Ostendorf CG, Wolf SL. Effect of forced use of the upper extremity of a hemiplegic patient on changes in function. Phys Ther 1981;61:1022–1028.
4. Taub E, Miller NE, Novack TA, et al. Technique to improve chronic motor deficit after stroke. Arch Phys Med Rehabil 1993;74:347–354.
5. Wolf SL, Winstein CJ, Miller JP, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial [see comment]. JAMA 2006;296:2095–2104.
6. Wolf SL, Winstein CJ, Miller JP, et al. Retention of upper limb function in stroke survivors who have received constraint-induced movement therapy: the EXCITE randomised trial. Lancet Neurol 2008;7:33–40.
7. Taub E, Uswatte G, Frank RG, Elliott TR. A New Approach to Treatment and Measurement in Physical Rehabilitation: Constraint-Induced (CI) Movement Therapy: Handbook of Rehabilitation Psychology. Washington, DC: American Psychological Association; 2000.
8. Biernaskie J, Chernenko G, Corbett D. Efficacy of rehabilitative experience declines with time after focal ischemic brain injury. J Neurosci 2004;24:1245–1254.
9. Dromerick AW, Edwards DF, Hahn M. Does the application of constraint-induced movement therapy during acute rehabilitation reduce hemiparesis after ischemic stroke? Stroke 2000;31:2984–2988.
10. Brott T, Adams HP, Olinger CP, et al. Measurement of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864–870.
11. Poole JL, Whitney SL. Motor Assessment Scale for stroke patients: concurrent validity and interrater reliability. Arch Phys Med Rehabil 1988;69:195–197.
12. Katzman R, Brown T, Fuld P, Peck A, Schechter R, Schimmel H. Validation of a short orientation-memory-concentration test of cognitive impairment. Am J Psychiatry 1983;140:734–739.
13. Mahoney F, Barthel D. Functional evaluation: the Barthel Index. Md Med J 1965;2:61–65.
14. Rankin J. Cerebral vascular accidents in patients over the age of 60: II: prognosis. Scott Med J 1957;2:200–215.
15. Halligan PW, Marshall JC, Wade DT. Visuospatial neglect: underlying factors and test sensitivity. Lancet 1989; 334:908–911.
16. Lyle RC. A performance test for assessment of upper limb function in physical rehabilitation treatment and research. Int J Rehabil Res 1981;4:483–492.
17. Granger CV, Hamilton BB, Linacre JM, Heinemann AW, Wright BD. Performance profiles of the Functional Independence Measure. Am J Phys Med Rehabil 1993;72:84–89.
18. Smith PM, Illig SB, Fiedler RC, Hamilton BB, Ottenbacher KJ, Fiedler RC. Intermodal agreement of follow-up

telephone functional assessments using the Functional Independence Measure in patients with stroke. Arch Phys Med Rehabil 1996;77:431–435.
19. Duncan PW, Wallace D, Lai SM, Johnson D, Embretson S, Laster LJ. The Stroke Impact Scale Version 2.0: evaluation of reliability, validity, and sensitivity to change. Stroke 1999;30:2131–2140.
20. Wong DL, Hockenberg-Eaton M, Wilson D, Winklestein ML, Schwarz P. Wong's Essentials of Pediatric Nursing. St. Louis: Mosby; 2001.
21. Yesavage JA. Geriatric Depression Scale. Psychopharmacol Bull 1988;24:709–711.
22. Meinert CL. Clinical Trials: Design, Conduct, and Analysis. New York: Oxford Press; 1986.
23. Lansberg MG, Thijs VN, O'Brien MW, et al. Evolution of apparent diffusion coefficient, diffusion-weighted, and T2-weighted signal intensity of acute stroke. AJNR Am J Neuroradiol 2001;22:637–644.
24. Wanklyn P, Forster A, Young J. Hemiplegic shoulder pain (HSP): natural history and investigation of associated features. Disabil Rehabil 1996;18:497–501.
25. van der Lee JH, Wagenaar RC, Lankhorst GJ, Vogelaar TW, Deville WL, Bouter LM. Forced use of the upper extremity in chronic stroke patients. Stroke 1999;30:2369–2375.
26. Boake C, Noser EA, Ro T, et al. Constraint-induced movement therapy during early stroke rehabilitation. Neurorehabil Neural Repair 2007;21:14–24.
27. Dobkin BH. Confounders in rehabilitation trials of task-oriented training: lessons from the designs of the EXCITE and SCILT multicenter trials. Neurorehabil Neural Repair 2007;21:3–13.
28. Page SJ, Levine P, Leonard AC. Modified constraint-induced therapy in acute stroke: a randomized controlled pilot study. Neurorehabil Neural Repair 2005;19:27–32.
29. Ching-yi W, Chia-ling C, Wen-chung T, Keh-chung L, Shih-han C. A randomized controlled trial of modified constraint-induced movement therapy for elderly stroke survivors: changes in motor impairment, daily functioning, and quality of life. Arch Phys Med Rehabil 2007;88:273–278.
30. Kozlowski DA, James DC, Schallert T. Use-dependent exaggeration of neuronal injury after unilateral sensorimotor cortex lesions. J Neurosci 1996;16:4776–4786.
31. Humm JL, Kozlowski DA, Bland ST, James DC, Schallert T. Use-dependent exaggeration of brain injury: is glutamate involved? Exp Neurol 1999;157:349–358.
32. Bland ST, Schallert T, Strong R, Aronowski J, Grotta JC. Early exclusive use of the affected forelimb after moderate transient focal ischemia in rats: functional and anatomic outcome. Stroke 2000;31:1144–1152.
33. Dromerick AW, Edwards DF, Kumar A. Hemiplegic shoulder pain syndrome: frequency and characteristics during inpatient stroke rehabilitation. Arch Phys Med Rehabil 2008;89:1589–1593.
34. Kraemer WJ, Ratamess NA. Fundamentals of resistance training: progression and exercise prescription Med Sci Sports Exerc 2004;36:674–688.
35. Sullivan KJ, Brown DA, Klassen T, et al. Effects of task-specific locomotor and strength training in adults who were ambulatory after stroke: results of the STEPS randomized clinical trial Phys Ther 2007;87:1580–1602.
36. Krakauer JW. Motor learning: its relevance to stroke recovery and neurorehabilitation. Curr Opin Neurol 2006;19:84–90.
37. Memmert D. Long-term effects of type of practice on the learning and transfer of a complex motor skill. Percept Mot Skills 2006;103:912–916.
38. Benveniste H, Hedlund LW, Johnson GA. Mechanism of detection of acute cerebral ischemia in rats by diffusion-weighted magnetic resonance microscopy. Stroke 1992;23:746–754.